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The Effect of Transfusions on the Incidence of Bacterial Infection

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The use of blood transfusions has been a art of medical practice for over half a century. The efficacy of blood and blood products in patients in hypovolemic shock from trauma or operative procedures has been well established. During the past quarter century, it has been demonstrated that blood transfusions administered prior to transplantation decrease the frequency and severity of allograft rejection. More recent work has indicated that this beneficial effect is the result of the transfusion inducing a state of immunosuppression in the recipient. A number of reports have suggested that this posttransfusion immunosuppression may result in an increased susceptibility to bacterial infections.

Blood transfusions became a clinical reality following Landsteiner's demonstration of three of the four main blood groups in 1900.[1] Subsequent to this discovery, the complications that resulted from the transfusion of incompatible red blood cells became avoidable and transfusion of blood and blood products became a reasonably safe and accepted treatment for severe anemias and life-threatening hemorrhage.[2]

Prior to the 1970s, many practitioners maintained that blood transfusions were immunostimulatory. This theory had its basis primarily on two observations. The first was the strong immunologic reaction resulting in lysis of red blood cells following the administration of incompatible red blood cells. The second observation was the demonstration by Medawar[2] that a more rapid rejection of skin allografts from a particular donor would occur if the recipient had previously been administered white blood cells obtained from that same donor.

A large number of retrospective human studies in the early 1970s, however, convincingly demonstrated that pretransplant transfusions actually decreased the frequency and severity of the immunologic rejection of transplanted kidneys.[3] The most significant contribution to this beneficial transfusion effect appears to be from suppression of the recipient's immune system, in contradistinction to the previously held belief in immunostimulation.[4]

The demonstration of decreased transplant rejection following transfusion led a number of investigators to examine whether transfusions would inhibit the body's immunologic response to tumors. Using rat models, both Francis and Shenton[5] and Waymack and Chance[6] demonstrated an increased rate of tumor growth in rats receiving whole-blood allogeneic transfusions but no significant change in rats receiving syngeneic transfusions. The need for an intact immune system to generate this posttransfusion effect was documented in a study by Francis et al.[7] that reported that this effect was not noted when athymic mice were employed. Waymack et al.[4] reviewed 13 reports in the literature designed to examine the effects of perioperative transfusion on the rate of metastases and tumor growth in patients undergoing oncologic surgery. These reports examined the effect of perioperative transfusions in patients with carcinomas of the colon, rectum, lung, and breast, as well as sarcomas. Nine of the 13 reports described increased rates of tumor recurrence and decreased long-term survival in those patients to whom perioperative transfusions were given. The other four series were unable to demonstrate any correlation. To respond to the possibility that a greater number of transfusions were required in patients with more advanced disease states, many of these studies further analyzed the effect of transfusions on patients within each tumor stage. They were again able to demonstrate a detrimental transfusion effect within these subgroups.

As a consequence of the demonstration of the immunosuppressive effects of blood transfusions in oncology and transplantation, there have been several recent investigations evaluating a possible relationship between the infusion of uncontaminated blood products and resistance to the development of bacterial infections. Some of the studies attempting to establish this relationship have used retrospective human data, while others have employed various animal models.

The initial animal report studied the effects of whole blood transfusions on mortality using a septic-burned rat model.[8] After subjecting nearly 300 rats to a 25% total body surface area scald burn, the animals were divided into groups that received either allogeneic blood tranfusions, syngeneic blood transfusions, or a comparable amount of lactated Ringer's solution prior to the burn. The burn wounds were painted with 1×10^8 *Pseudomonas aeruginosa*. Allogeneic transfusions were found to decrease significantly the mean survival time and absolute survival rate unless the blood was given within the 24 hours prior to the *Pseudomonas aeruginosa* challenge. No significant survival changes were recorded in those rats receiving syngeneic blood transfusions.

A further investigation into the effect on mortality of the number and volume of transfusions was also carried out in an animal model.[9] Rats were subjected to a 30% total body surface area full-thickness scald burn, which was painted with *Pseudomonas aeruginosa* on the first postburn day. The infected rats had previously received lactated Ringer's alone (control group), a single 0.1-ml allogeneic blood transfusion, a single

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1.0-ml allogeneic blood transfusion, or three 1.0-ml allogeneic transfusions. In this manner, the amount of blood transfused was varied 30-fold. The mean survival times and absolute survival rates were recorded. The findings revealed that each group of transfused rats had a significantly increased mortality rate when compared with the control group. Statistical differences between the various transfusion groups were not found, indicating that there does not appear to be a significant additive immunosuppressive effect of transfusions in this model.

Studies using another animal model examined the effect of blood transfusions on resistance to bacterial peritonitis.[10] Rats received 0.5 ml of allogeneic blood, 0.5 ml of syngeneic blood, or 1.5 ml of normal saline (control group). They were then challenged with intraperitoneal injections of an *Escherichia coli* suspension on the day of transfusion or 4 days posttransfusion. The results demonstrated a statistically significant decrease in survival in rats receiving allogeneic transfusions, irrespective of the timing of the septic challenge. No statistically significant differences were noted in those rats receiving transfusions from syngeneic rats when compared with saline controls.

There are a number of retrospective studies in the literature that suggest that blood transfusions result in a decreased resistance to bacterial infections in humans as well. Tartter et al.[11] examined the relationship of perioperative blood transfusions to infectious complications following operations for colorectal cancer. One hundred and sixty-eight consecutive patients without clinical evidence of metastases scheduled for elective colorectal cancer operations were evaluated for infectious complications. They noted a 25% incidence of infectious complications in patients who received perioperative blood transfusions. Those patients not receiving perioperative transfusions had an incidence of only 7%, which was statistically significant ($p = .01$). Perioperative blood transfusions were found to be associated with an increased incidence of infectious complications, regardless of whether they were given preoperatively, intraoperatively, or postoperatively. Also, the mean number of transfusions administered correlated with increased infectious complications to a statistically significant degree. Patients who developed such complications received an average of 2.14 units of blood, versus .82 units in those patients without complications ($p = .0005$). Other variables that were examined and found not to show any significant differences between infected and noninfected patients included age, sex, operative procedure, tumor differentiation, tumor stage, positive lymph nodes, specimen size, and tumor size.

In a more recent report, Tartter et al.[12] examined the relationship between blood transfusions and postoperative infectious complications in patients with Crohn's disease. Their results noted postoperative septic complications in 26% of patients receiving two or more units of blood as compared with an 8% infection rate in those patients receiving one unit of blood or no blood. This difference was statistically significant ($p = .0014$). Subgroup and multivariate analyses of various other factors were carried out, including the variables of age, sex, percent ideal body weight, duration of disease, previous surgery, preoperative steroid use, type of resection employed, and creation of ileostomy. None of these variables demonstrated a significant difference with regard to development of postoperative infectious complications.

In a multi-institutional study of patients with penetrating abdominal trauma, blood transfusion was again identified as an independent risk factor in the development of postoperative infectious complications.[13] This prospective study demonstrated that the number of units of blood given was significantly associated with the development of postoperative infections independent of other variables such as advanced age, number of injured organs, or colostomy.

In unpublished data, Graves et al.[14] reviewed patients with 10% to 70% total body surface area burns treated at this Institute from 1982–86. Their findings revealed that transfusions were associated with an increased incidence of burn wound infection and pneumonias. Other factors noted to have contributing effects in this study were patient age and burn size.

Dellinger et al.[15] prospectively examined patients with open extremity fractures for the risk of developing postoperative infections. In patients receiving perioperative blood transfusions, there was a 20% infection rate; those patients who did not receive transfusions had an 8% infection rate ($p < .05$).

These studies appear to indicate an increased susceptibility to bacterial infections following transfusion. Investigations to disclose possible mechanisms for the increased susceptibility in both animal models and humans have been undertaken, and a number of possible etiologies have been identified.

Stephan et al.[16] used a rat model to document a significant (70%) decrease in the ability of splenocytes to generate interleukin 2 following single or multiple blood transfusions when compared with controls. The decreased interleukin 2 production was more profound after multiple transfusions, returning to near normal by posttransfusion day 7 in singly transfused rats and remaining profoundly depressed (18% of control) on posttransfusion day 7 in multiply transfused rats. The ability of peritoneal macrophages to maintain normal antigen presentation function, which has been shown to be defective in the face of trauma or tumor,[17,18] was not adversely affected by the use of blood transfusions.

Two studies have shown that allogeneic blood transfusions in rats are associated with a greater than twofold increase in the production of prostaglandin E by macrophages.[19,20] Prostaglandin E is a metabolite of arachidonic acid and is probably the most immunosuppressive of all the metabolites, having been demonstrated to impair T-cell blastogenesis following mitogen stimulation,[21] impair macrophage differentiation and phagocytosis,[22] and impair the ability of mononuclear cells to lyse tumor cells.[23] Blood transfusions apparently fail to increase macrophage production of leukotrienes, a group of arachidonic acid metabolites of the lipooxygenase system, which exert an immunostimulatory effect on several components of the immune system.[24]

It has further been documented that transfusion induces a diminished macrophage migration response following the induction of a sterile peritonitis.[24,25] This finding was statistically significant in rats receiving allogeneic transfusions, but not so in rats receiving syngeneic transfusions. Cell-mediated immunity has been shown to be impaired in rats receiving blood transfusions.[24] Those animals receiving tranfusions demonstrated a significant suppression of cell-mediated immunity as measured by skin swelling in response to topical application of 0.5% dinitrofluorobenzene. Finally, it has been shown that

macrophages obtained from allogeneically transfused rats can impair the normal lymphocyte blastogenic response to mitogen stimulation.[25]

Similar immunologic assays have been performed in patients with blood dyscrasias who require transfusions. These studies have documented a decreased CD4/CD8 (helper/supressor) T-lymphocyte ratio following transfusion.[26,27] It has also been demonstrated that transfusion impaired natural killer cell function.[27]

It is frequently necessary to transfuse patients due to life-threatening anemias or blood loss. In such patients, it would be desirable to be able to transfuse the patient without causing posttransfusion immunosuppression. One such method would be to have patients donate a unit or more of blood in the weeks prior to their scheduled surgery (autologous donation). If they sustained a significant blood loss at the time of surgery, they could then receive their own blood (the immunologic equivalent of a syngeneic transfusion). Such a transfusion should not result in any immunosuppression. Unfortunately, this solution is only feasible in elective surgical procedures. Another feasible approach is the use of frozen washed red blood cells that lack foreign histocompatibility antigens, since these antigens are apparently responsible for posttransfusion immunosuppression.[28] Finally, the use of intraoperative autologous transfusion devices that collect blood losses from the operative field, wash the blood, and then return it to the patient intravenously may allow correction of blood losses without exposing the patient to foreign white blood cell antigens.

In conclusion, blood transfusions appear to result in immunosuppression in the transfusion recipient as a consequence of exposure to foreign human leukocyte antigens. This immunosuppression may predispose the recipient to infectious complications and increased tumor growth and metastases. Methods of correcting blood loss without causing immunosuppression are currently being investigated.

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